IN SILICO SCREENING AND MOLECULAR DOCKING STUDIES OF INDENOISOQUINOLINE DERIVATIVES AS POTENT TOPOISOMERASE I INHIBITOR USING INDUCED FIT DOCKING

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ABSTRACT:

The present study was aimed to evaluate the Indenoisoquinoline derivatives as potent anticancer inhibitor using computational docking programs. Indenoisoquinoline is a novel lead molecule for the inhibition of Topoisomerase 1(Top1) which is important for the successful replication, transcription, recombination, repair and chromosome decondensation. Two series of Indenoisoquinoline Top 1 inhibitors are nitrated Indenoisoquinolines and 2,3 dimethoxy-substituted Indenoisoquinoline derivative compounds of 112 was subjected to analyse the interaction and inhibitory actions with target Top 1. The *in silico* high throughput virtual screening (HTVS) and Induced Fit Docking (IFD) studies revealed most of the Indenoisoquinoline derivatives possess interactions with the active site residues ARG364, ASN722 and DC112 of Top1 enzyme. The result of docking analysis provides the detailed structural insight as well as highlighted the important binding features of Indenoisoquinoline derivatives and can be developed as potent topoisomerase inhibitors.

Index terms - Indenoisoquinoline deravatives, Top 1, ARG364, GLIDE and Induced Fit Docking.

I. INTRODUCTION

DNA topoisomerases are enzymes that regulate the conformational changes in DNA topology and plays critical roles in many biological processes involving DNA. There are two types of DNA topoisomerases Top1 and Top 2. Top 1 make a transient break in one strand of DNA and Top1 structure is bound to the oligonucleotide sequence 5'-AAAAA GACTTsX-GAAAAATTTTT-3', where "s" is the 5'-bridging phosphorothiolate of the cleaved strand and "X" represents any of the four bases A, G, C or T [1]. Human Topoisomerase 1 contains four major domains i) a domain which is highly charged and unconserved in the NH2 terminal (with residues MET1-LYS197), ii) A conserved core domain constituted by the residues GLU198-ILE651, iii) a short positively charged unconserved linker domain with residues ASP652-GLU696 and iv) a highly conserved domain at COOH terminal with residues from GLU697-PHE765 having active hydrophobic TYR723 in it [2]. The catalytic residue of human DNA topoisomerase 1 are ASN352, ARG364, LYS532, ASP533, ASN722 and TYR723.

Many cancer type-specific anticancer agents have been developed and significant advances have been made toward precision medicine in cancer treatment. Clinical validation of Top 1 as a drug target for camptothecin derivatives topotecan and irinotecan representing the only top 1 inhibitors approved by the U. S. Food and Drug Administration for anticancer therapy. Camptothecins are effective topoisomerase I inhibitors approved for cancer treatment; hence the present study selected the 112 indenoisoquinolines derivatives form [3] to understand the inhibitory mode of indenoisoquinoline with Top 1-DNA complexes by predicting the anticancer activity on the basis of docking score. The current work was analysed to find better interactions for the compounds using HTVS (High Throughput Virtual Screening) and induced fit docking studies.

II. MATERIALS AND METHODS:

Retrieval and Preparation of the Protein: The experimental structure of human DNA topoisomerase (Top 1) complexed with inhibitor indenoisoquinoline (M38) has been retrieved from the Protein Data Bank with the ID 1SC7. The active site of the enzyme was identified using PDBSUM, LIGPLOT and literature review.

Retrieval of the Ligand: The ligand molecules selected for the present study was based on the scientific report of Morrell et al., 3 which were drawn using ACD / ChemSketch. Fig. 1 shows the structure of the sketched compounds. Further the indenoisoquinolines was subjected for energy minimization in Argus lab.

HTVS and Induced Fit Docking: The virtual screening workflow (Maestro, Schrodinger, 2009) was used to identify potential derivative against Top1. A total of 112 compounds were carried out through high throughput virtual screening (HTVS). Glide HTVS, Standard Precision, and Extra Precision parameters were checked and set to save 20% of the good scoring ligands. Finally, top most five lead compounds were screened based on Glide score, Glide energy, and hydrogen bond interactions and best hit compounds were selected for IFD analysis. Here, Van der Waals radii of non-polar atoms of the receptor and ligand were scaled by a factor of 0.50, and 20 conformational poses were calculated. Based on the docking score, Glide energy, Glide emodel and non-bonded interactions best compounds were selected and analysed through IFD.

III. RESULT AND DISCUSSION:

To find the binding affinity and key interactions between the two series of indenoisoquinolines and Top1-DNA complex receptor, High Throughput Virtual Screening (HTVS) and Induced-Fit Docking (IFD) studies was carried out using Glide module form Schrodinger. The ligands and co-crystal were docked in the active site of optimized and energy minimized Top 1 and the results were analysed to identify the potential compound with better score and hydrogen bond interactions for top ranked possess. The active site residues of Top1 were selected from the ligplot, pdbsum and literature viz. ALA351, ASN352, ARG364, LYS532, ASP533, ASN722 and TYR723.

Most widely used methods for virtual high throughput screening is docking of small molecules into active site of protein target and subsequent scoring. The binding was screened against the top1 protein using screening workflow. The Glide HTVS was performed with flexible docking algorithm using selected constraints for each grid in OPLS 2005 force field [4]. Using Glide HTVS, about 112 compounds were screened from binding. The stability of the top rank docked pose of the ligand molecules were evaluated based on the hydrogen bond interaction of the active site amino acid of the protein with the compound [5]. Screening results in 5 compounds which have higher binding affinity towards top1 (Table 1). From HTVS results five compounds were selected, the compounds 34, 47, 48, 86 and 94 showed better glide score (Kcal/mol) -8.87, -7.64, -8.86, -8.46 and -7.01, respectively than the co crystal -7.30. The selected compounds possess interaction with the active site residue ARG364. The energy minimized, top-ranked poses of docked complexes of top1 with the selected inhibitors were intercalated readily at the DNA cleavage site, between the base pair, scissile strand base and non-cleaved strand base. [6] designed, synthesized and docked the morpholine derivatives with Top1-DNA complex which showed Top1 inhibitory activity by binding with the important residues ARG364. The compounds 34, 48, 47 and 94 possess interaction with ARG364 of top1 using GOLD software [7].

Further all the screened compounds were subjected for IFD, one of the main complicating factors predicts accurate ligand binding modes and concomitant structural movements in the receptor using modules of Glide and Prime. Frome the IFD results, the compounds 47, 48 and 94 showed best conformation with docking score, glide energy and hydrogen bond interactions than the co-crystal (Table 2).

Structures of topoisomerase-drug-DNA ternary complexes have revealed the exact binding sites and mechanisms of Indenoisoquinoline Derivatives. The IFD complex of compound 47, 48 and 94 with top1 had H-bond interaction with the active site residue ARG364 (Table 3). The X-ray crystal structure of ternary campthothecin - Top1 -DNA complex indicated that camptothecin intercalated at the site of DNA cleavage and formed 2 hydrogen bonds with the active site residue ARG364 and ASP533 (Staker *et al*., 2005). The compound 47, 48 and 94 had better score of -8.12, -7.79 and -8.35, respectively than the co-crystal 4-(5, 11-Dioxo-5H-indeno [1, 2-c] isoquinolin-6 (11H)- yl) butanoate. Additionally the compounds 48 and 94 had interaction with ASN352, DC112 and ASN722, respectively (Table 2). Kumar and Bora, (2014) analysed molecular docking studies of curcumin derivatives with Top1-DNA complex as a potential lead molecule for the development of inhibitor for targets Top1. The cyclocurcumin play an important role in binding at the site of DNA cleavage and that had interactions with ARG364, ASN722 and base A113. The results of the present study revealed the efficiency nitrated indenoisoquinoline and dimethoxysubstitued indenoisoquinoline derivatives that interacted with the important residues ARG364 which were identified to have interactions with the inhibitors in the complexed structure.

Figure 1: Two series of selected Indenoisoquinoline

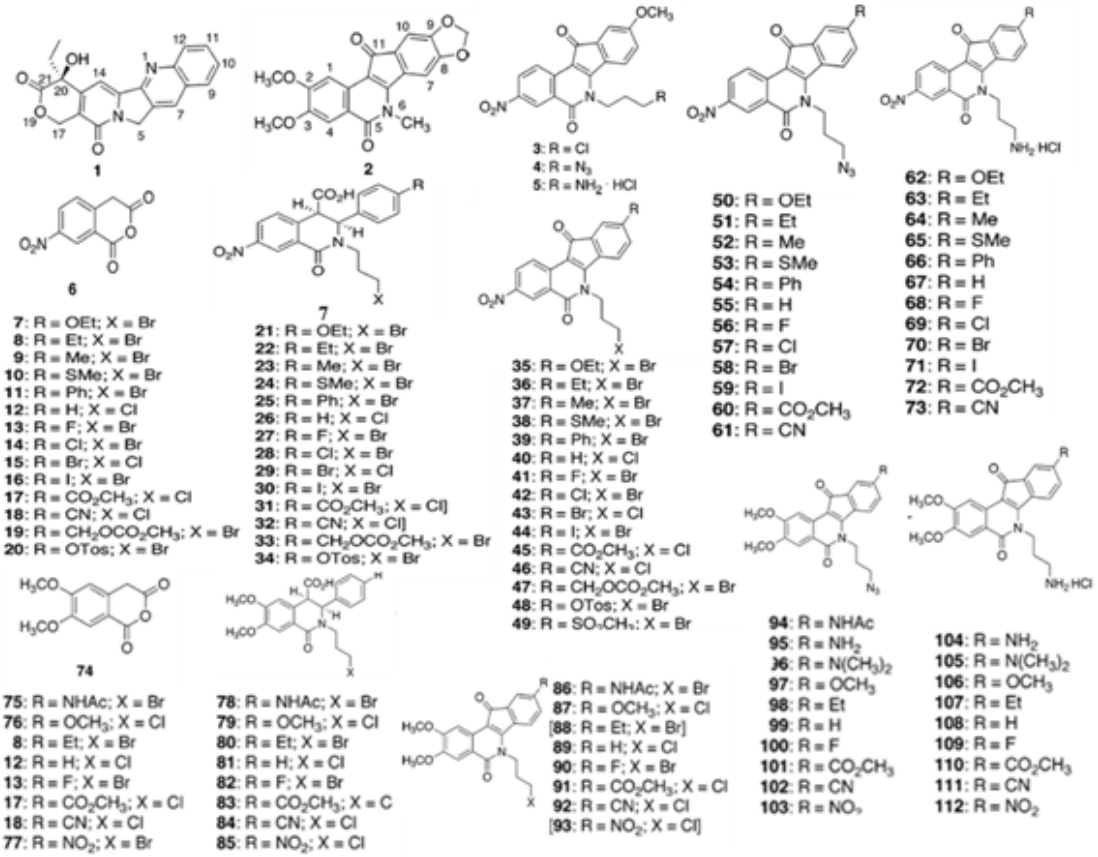


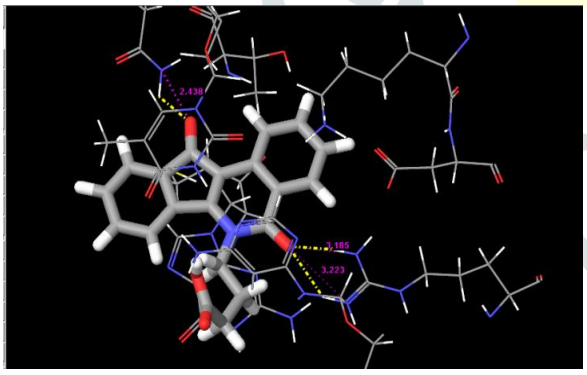
Table 1.Co-crystal and selected lead compounds from HTVS

S.no	Compound	Glide score (Kcal/mol)	Glide Energy (Kcal/mol)	Interaction (D-H…A)	H-bond length (Å)
1	Co-Crystal	-7.30	-51.44	(DA113) O-H...O (ARG364) N-H...O	3.012 2.845
2	Compound 34	-8.87	-52.87	(ASN722)N-H...O (DT10) N-H...O	2.955 2.772
3	Compound 47	-7.64	-54.94	(ASN722) N-H...O (ARG364) N-H....O (ARG364) N-H....O	2.955 2.712 2.807
4	Compound 48	-8.86	-61.73	(MET428) N-H...O (ASN722) N-H...O (ARG364) N-H...O	2.991 2.895 2.709
5	Compound 86	-8.46	-60.45	(ARG364) N-H...O (ASN722)N-H...O (ARG364) N-H...O	3.144 2.965 2.736
6	Compound 94	-7.01	-62.03	(ARG364) N-H...O (ASP533)N-H...O (ARG364) N-H...O	3.114 2.934 2.757

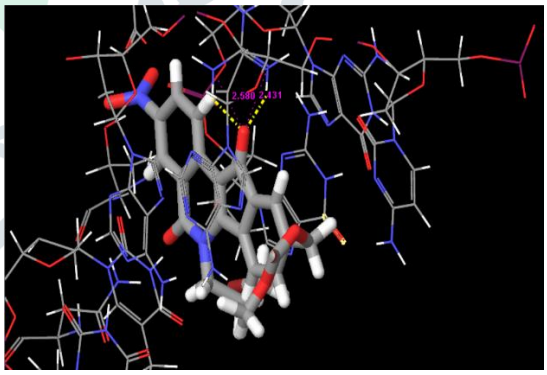
Table 2. Glide score, glide energy and interacting residues from Induced Fit Docking

S.no	Compound	Glide Score (Kcal/mol)	Glide Energy (Kcal/mol)	Interaction (D-H…A)	H-bond length (Å)
1	Co-Crystal	-7.19	-49.85	(ARG364) N-H...O (ARG364) N-H...O (ASN722) N-H...O	3.223 3.185 2.438
2	Compound 47	-8.21	-50.97	(ARG364) N-H...O (ARG364) N-H...O	2.580 2.431
3	Compound 48	-7.79	-53.06	(ARG364) N-H...O (ASN352) N-H....O (DC112) N-H...O	2.709 2.307 2.271
4	Compound 94	-8.35	-83.28	(ASN722) N-H...O (ARG364) N-H...O (ARG364) N-H...O	2.970 2.629 2.167

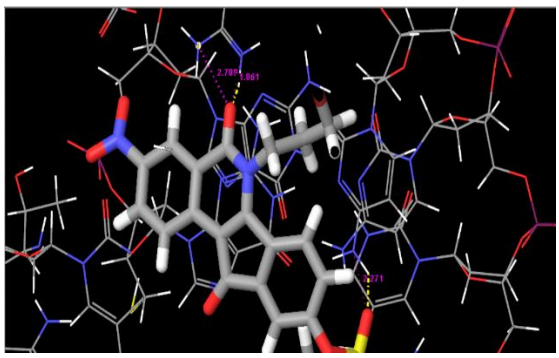
Table 3. Interactions of the ligand molecules with Top1 from IFD



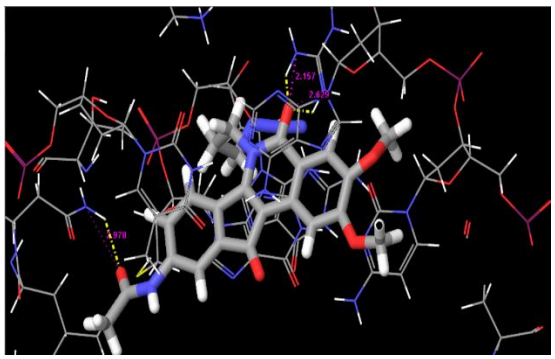
Co-Crystal



Compound 47



Compound 48



Compound 94

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